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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
HUYNH, PHUONG N	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,501	OGATA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/9/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,12-17,19-22,25,26 and 28* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,16,19-22,25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4-10, 12-17, 19-22, 25-26 and 28 are pending.

2. Claims 12-15 and 17 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 4-10, 16, 19-22, 25-26 and 28, drawn to a method of maintaining or increasing low vasopressin level, a method of treating at least one symptom caused by a decrease in vasopressin level and a method of inhibiting the binding between PTHrP and a receptor thereof comprising administering to the patient at least one anti-PTHrP antibody or binding fragment thereof, are being acted upon in this Office Action.

4. In view of the amendment filed 7/9/07, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 4-10, 16, 19-20, 25-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of ameliorating the low blood vasopressin level or treating a symptom caused by a decrease in blood vasopressin level by administering to a patient at least one antibody or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 or a monoclonal antibody produced by the hybridoma deposited as FERM BP-5631 or a humanized antibody, a chimeric antibody, or binding fragment thereof, and polyethylene glycol (PEG) conjugated antibody thereof, **does not** reasonably provide enablement for any methods as set forth in claims 4-10, 16, 19-22, 25-26 and 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731,

737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 9-10 encompass a method of treating at least one symptom caused by a decrease in any vasopressin level by administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof, that inhibits the binding between PTHrP and a receptor thereof.

Claims 19 and 20 encompass a method of inhibiting the binding between PTHrP and a receptor thereof comprising "providing" an anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof wherein the antibody is any modified antibody having any amino acid substitution, or any chemical modification, or any human antibody that specifically binds to SEQ ID NO: 75.

Claims 25-26, and 4-8 encompass a method of maintaining or increasing low vasopressin level comprising administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody such as monoclonal antibody humanized, human, chimeric antibody, or any antibody having any modified antibody having any amino acid substitution, or any chemical modification, or any human antibody that specifically binds to SEQ ID NO: 75, or binding fragment thereof such as Fab scFv, F(ab')2, or Fv or polythelylene glycol (PEG) conjugated antibody that inhibits the binding between PTHrP and a receptor thereof, allowing the antibody to inhibit the binding of PTHrP and its receptor, and maintaining or increasing vasopressin level, wherein the antibody, or binding fragment thereof, binds specifically to SEQ ID NO: 75, and wherein the antibody neutralizes parathyroid hormone related protein 1-34.

The specification discloses a method treating low blood vasopressin level by administering to a patient a monoclonal or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, see page 23-23, Figure 1. The monoclonal antibody #23-57-137-1 that binds specifically to N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 is produced by hybridoma deposited as FERM BP-5631. The deposit has been made under the terms of the Budapest Treaty on August 15, 1996 at the National Institute of Bioscience and

Human-technology Agency of Industrial Science and Technology, Japan (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan) under the accession No. FERM BP-5631 as indicated at page 24. A declaration by Masao Haruna filed October 20, 2004, who is associated with the patent owner, stating that the hybridoma FERM BP-5631 secreting the antibody #23-57-137-1 has been deposited under the Budapest Treaty and that said hybridoma FERM BP-5631 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent had satisfied the deposit requirement made herein. The specification further discloses a method of making chimeric or humanized #23-57-137-1 thereof that binds specifically to human PTHrP 1-34 consisting of the amino acid sequence of SEQ ID NO: 75 for inhibits the binding of PTHrP to its receptor and thereby ameliorates the low blood vasopressin levels associated with cancer such as mice implanted with human large cell lung carcinoma LC-6, which is a human hypercalcemia model (see Figure 1). The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses the specific amino acid substitutions in the light chain of monoclonal antibody #23-57-137-1 such as the ones disclosed at page 62 for making humanized antibody.

With respect to claims 9-10, the specification discloses a method of treating at least one symptom caused by a decrease in *blood* vasopressin level by administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof, that inhibits the binding between PTHrP and a receptor thereof, see page 3 line 12. Amending claim 9 to recites " a decrease in blood vasopressin level" would obviate this rejection.

The specification does not teach a method of treating at least one symptom caused by a decrease in *any* vasopressin level by administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof, that inhibits the binding between PTHrP and a receptor thereof. This is because vasopressin levels could be found in different tissue such as the posterior pituitary gland in the brain.

With respect to antibody any modified antibody having any amino acid substitution (claims 4 and 19), the antibody in said claims encompass any amino acid substitution including the immunoglobulin heavy and light chain CDRs as well as framework region.

The specification exemplifies humanized antibody having the specific substitution in the framework regions of the immunoglobulin light chain, see example 5, pages 67-69. The specification discloses conjugating to polyethylene glycol to extend the half-life of the antibody or antibody fragment.

Other than humanized antibody having the specific amino acid substitution at the specified position and pegylation, the specification does not teach how to make any modified antibody having any amino acid substitution or any chemical modification such that the modified antibody still binds specifically to SEQ ID NO: 75 for the claimed methods. There is insufficient guidance and *in vivo* working example as to which amino acids within the full-length sequence of immunoglobulin heavy and light chains of which anti-PTHrP antibody or binding fragment thereof to be substituted such that the modified antibody or binding fragment still binds specifically to SEQ ID NO: 75, let alone under which condition that administering such antibody increases vasopressin in blood or in the brain or any other organ or maintaining vasopressin levels in blood or in other tissues.

The state of the prior art as exemplified by Abaza *et al*, of record, is such that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of a protein with monoclonal antibody against the site (See abstract, in particular).

Given the unlimited number of amino acid substitution, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin level and whether the vasopressin levels in blood vasopressin levels or tissue specific vasopressin levels. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to antibody any modified antibody having any chemical modification (claims 4 and 19), the specification discloses conjugating antibody to polyethylene glycol; PEG), see page 13 at last line. The specification does not teach any chemically modified antibody. It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody.

The state of the prior art as exemplified by Banerjiee et al (J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al

teach disrupting interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to protein (see abstract, page 5141, col. 2, first paragraph, in particular).

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended to limited to antibody. The instant application provides ample guidance for synthesizing modified antibodies comprising amino acid substitutions or chemical modifications. *See, e.g.,* Reference Example 4, pp. 47-67; and p. 13, In. 28-p. 14, In. 4. Moreover, the specification teaches assays for determining whether the modified antibodies retain antigen-binding function and neutralizing activity. *See, e.g.,* Reference Example 4, pp. 47-67 and Reference Example 5, pp. 67-69. Finally, Applicants have provided examples of nineteen modified antibodies and have disclosed the regions of these antibodies which tolerate modification. Specifically, nineteen modified antibodies, comprising 50 amino acid substitutions are exemplified. *See, e.g.,* Reference Example 4, pp. 47-67. In addition, the specification

teaches regions of the antibodies which tolerate modification and exemplary modifications that result in wild-type neutralizing activity. *Id.* and Reference Example 5, pp. 67-69. Under the standard established in *Angstadt,* Applicants need not demonstrate each and every operable embodiment of claims 4 and 19. Rather, the test is whether undue experimentation is required to make and screen the embodiments. In view of the ample guidance provided by the specification, Applicants submit that the ordinary artisan could practice the inventions of claim 4 and currently amended claim 19 without undue experimentation. Accordingly, Applicants respectfully request that the enablement rejection of claims 4 and 19 be withdrawn.

In response, Claims 9-10 encompass a method of treating at least one symptom caused by a decrease in any vasopressin level by administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof, that inhibits the binding between PTHrP and a receptor thereof.

The specification discloses a method of treating at least one symptom caused by a decrease in *blood* vasopressin level by administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof, that inhibits the binding between PTHrP and a receptor thereof, see page 3 line 12. Amending claim 9 to recites " a decrease in blood vasopressin level" would obviate this rejection.

With respect to any modified antibody having any amino acid substitution (claims 4 and 19), the antibody in said claims encompass any amino acid substitution including the immunoglobulin heavy and light chain CDRs as well as framework region.

The specification exemplifies humanized antibody having the specific substitution in the framework regions of the immunoglobulin light chain, see example 5, pages 67-69. The specification discloses conjugating to polyethylene glycol to extend the half-life of the antibody or antibody fragment.

Other than humanized antibody having the specific amino acid substitution at the specified position and pegylation, the specification does not teach how to make any modified antibody having any amino acid substitution or any chemical modification such that the modified antibody still binds specifically to SEQ ID NO: 75 for the claimed methods.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions

of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979; PTO 892). Enclosed evidentiary reference Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Wu et al. (J. Mol. Biol.294 : 151-162, 1999 ; PTO 892) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Given the unlimited number of amino acid substitution, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin and whether the vasopressin levels in blood vasopressin levels or tissue specific vasopressin levels. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to antibody any modified antibody having any chemical modification (claims 4 and 19), the specification discloses conjugating antibody to polyethylene glycol; PEG), see page 13 at last line. The specification does not teach any chemically modified antibody. It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody.

The state of the prior art as exemplified by Banerjiee et al (J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and

alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al teach disrupting interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to protein (see abstract, page 5141, col. 2, first paragraph, in particular).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 4-10, 16, 19-22 and 26 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892).

The '194 patent teaches a method of treating a symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low vasopressin levels (see col. 1, lines 42-61, in particular). The reference method inhibits the binding of PTHrP to its receptor by administering to a patient an anti-PTHrP antibody such as a monoclonal antibody, humanized antibody, chimeric antibody and/or human antibody thereof that binds to human PTHrP 1-34, wherein the reference human PTHrP 1-34 is 100% identical to the claimed SEQ ID NO: 75 (see entire document, claim 11 of the '194 patent, col. 7, lines 41-57, reference SEQ ID NO: 75, col. 3, lines 64-65, col. 14, lines 56, claims 1-6 of

the '194 patent, col. 10, lines 60-67, col. 30, lines 50, col. 24, lines 10, in particular). The reference monoclonal antibody #23-57-1371 is produced by hybridoma deposited under accession No. FERM BP-5631 (see col. 27, lines 29-36, in particular). The '194 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). The '194 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the humanized #23-57-137-1 in the claimed method (see col. 24, line 15, in particular).

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see col. 2, lines 42-52, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that the '194 patent does not inherently teach methods of maintaining or increasing vasopressin levels, as required by claims 4-10, 16, 19-22 and 26. There is nothing in the record to demonstrate that any of the hypercalcemia patients discussed in the '194 patent were suffering from low vasopressin levels. The '194 patent does not mention vasopressin levels or the effect of an anti-PTHrP antibody on vasopressin level. Thus, the Office has not provided a basis in fact and/or technical reasoning to support its position that "the reference method inherently has the same effect as maintaining low vasopressin level as claimed." Office Action at p. 15. Without such support, it is impossible to state that administration of a PTHrP antibody necessarily maintained or increased the low vasopressin levels. The unlikely and purely coincidental possibility that some patients may be suffering from both hypercalcemia

and low vasopressin level and that both conditions may be treated by administration of a PTHrP antibody does not legally suffice to show anticipation.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether it is blood vasopressin or tissue specific vasopressin level.

The '194 patent teaches a method of treating a symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low vasopressin levels (see col. 1, lines 42-61, in particular). Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see col. 2, lines 42-52, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

10. Claims 4-10, 16, 19-22 and 26 stand rejected under 35 U.S.C. 102(b) as being anticipated by CA 2,266,332 publication (published April 2, 1998; PTO 892).

The CA 2,266,332 patent teaches a method of treating at least one symptom caused by a decrease in vasopressin levels as a results from cancer such as polyuria and dehydration (see page 2, lines 7-24, page 135, in particular) by administering to patient such as animal or human (see page 49, lines 1-14, in particular) at least one anti-PTHrP such as monoclonal antibody, chimeric or humanized antibody (see page 14, page 55, page 76, in particular) and/or human antibody thereof (see claim 46 of the CA 2,266,332 patent, in particular) that binds specifically to human PTHrP1-34 of SEQ ID NO: 75, which is which is 100% identical to the claimed SEQ ID NO: 75 (see paragraph bridging

pages 14-15, in particular). The CA 2,266,332 patent teaches monoclonal antibody #23-57-1371 produced by deposited hybridoma FERM BP-5631 (see page 55, line 4, in particular) and humanized antibody #23-57-1371 (see page 49, page 103, and pages 118, 121, in particular). The CA 2,266,332 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the immunoglobulin light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see Table 3 at page 103, paragraph bridging page 97 and 98, in particular). The CA 2,266,332 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the claimed humanized #23-57-137-1.

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see page 2 of CA266,332, lines 7-24, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that the CA 2,266,332 patent does not inherently teach methods of maintaining or increasing vasopressin levels, as required by claims 4-10, 16, 19-22 and 26. There is nothing in the record to demonstrate that any of the hypercalcemia patients discussed in the CA 2,266,332 patent were suffering from low vasopressin levels. The CA 2,266,332 patent does not mention vasopressin levels or the effect of an anti-PTHrP antibody on vasopressin level. Thus, the Office has not provided a basis in fact and/or technical reasoning to support its position that "the reference method inherently has the same effect as maintaining low vasopressin level as claimed." Office Action at p. 15. Without such support, it is impossible to state that administration of a PTHrP antibody necessarily maintained or increased the low vasopressin levels. The unlikely and purely coincidental possibility that some patients may be suffering from

both hypercalcemia and low vasopressin level and that both conditions may be treated by administration of a PTHrP antibody does not legally suffice to show anticipation.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level.. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether it is blood vasopressin or tissue specific vasopressin level.

The CA 2,266,332 patent teaches a method of treating at least one symptom caused by a decrease in vasopressin levels as a results from cancer such as polyuria and dehydration (see page 2, lines 7-24, page 135, in particular) by administering to patient such as animal or human (see page 49, lines 1-14, in particular) at least one anti-PTHrP such as monoclonal antibody, chimeric or humanized antibody (see page 14, page 55, page 76, in particular) and/or human antibody thereof (see claim 46 of the CA 2,266,332 patent, in particular) that binds specifically to human PTHrP1-34 of SEQ ID NO: 75, which is which is 100% identical to the claimed SEQ ID NO: 75 (see paragraph bridging pages 14-15, in particular). The CA 2,266,332 patent teaches monoclonal antibody #23-57-1371 produced by deposited hybridoma FERM BP-5631 (see page 55, line 4, in particular) and humanized antibody #23-57-1371 (see page 49, page 103, and pages 118, 121, in particular). The CA 2,266,332 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the immunoglobulin light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see Table 3 at page 103, paragraph bridging page 97 and 98, in particular). The CA 2,266,332 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the claimed humanized #23-57-137-1.

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see page 2 of CA266,332, lines 7-24, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of

symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 4, 9-10, 16, 19, 25-26 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level

comprising administering to the patient a modified form of the anti-PTHrP antibody fragment instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any

antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that binds specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining low or increasing vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules leas to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that Kitamura, which teaches a PEG-conjugated antibody fragment, does not discuss modulating vasopressin levels and thus, fails to cure the defect in the '194 patent and the '332 patent.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether is it blood vasopressin or tissue specific vasopressin level.

The teachings of the '194 patent have been discussed supra.

The claimed invention differs from the teachings of the patent only in that the antibody or binding fragment thereof is conjugated to PEG. Kitamura, which teaches a PEG-conjugated antibody fragment. Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular).

14. Claims 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,903,194 (of record, filed March 25, 1999: PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the monoclonal, human antibody, chimeric or humanized PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP

and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that Kitamura, which teaches a PEG-conjugated antibody fragment, does not discuss modulating vasopressin levels and thus, fails to cure the defect in the '194 patent and the '332 patent.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether is it blood vasopressin or tissue specific vasopressin level.

The teachings of the '194 patent have been discussed supra.

The claimed invention differs from the teachings of the patent only in that the antibody or binding fragment thereof is conjugated to PEG. Kitamura, which teaches a PEG-conjugated antibody fragment. Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse

monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular).

15. Claims 4, 9-10, 16, 19, 25-26 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (published April 2, 1998; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP of SEQ ID NO: 75 is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side-effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising administering to the patient a binding fragment of an anti-PTHrP antibody instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that

binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that binds specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining low vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the CA 2,266,332 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody

fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that Kitamura, which teaches a PEG-conjugated antibody fragment, does not discuss modulating vasopressin levels and thus, fails to cure the defect in the '194 patent and the '332 patent.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether is it blood vasopressin or tissue specific vasopressin level.

The teachings of the '332 patent have been discussed supra.

The claimed invention differs from the teachings of the patent only in that the antibody or binding fragment thereof is conjugated to PEG. Kitamura, which teaches a PEG-conjugated antibody fragment. Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular).

16. Claims 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (published April 2, 1998; PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human

PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using any antibody such as monoclonal, human antibody, chimeric or humanized antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the CA 2,266,332 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in

particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

Applicants' position is that Kitamura, which teaches a PEG-conjugated antibody fragment, does not discuss modulating vasopressin levels and thus, fails to cure the defect in the '194 patent and the '332 patent.

In response, claim 26 as written is unclear as to under which condition that when administering anti-PTPrP1-34 to a patient, it maintains vasopressin levels and if maintain, whether it is blood vasopressin or tissue specific vasopressin level. Further, is unclear as to under which condition that administering anti-PTPrP1-34 to patient increases vasopressin levels in which patient population and if maintain, whether is it blood vasopressin or tissue specific vasopressin level.

The teachings of the '332 patent have been discussed supra.

The claimed invention differs from the teachings of the patent only in that the antibody or binding fragment thereof is conjugated to PEG. Kitamura, which teaches a PEG-conjugated antibody fragment. Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular).

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d

1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

18. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 4-10, 16, 18, 20-22 and 26 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. US Pat No 6,903,194 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issuance of a patent to instant claims which drawn to a method of inhibiting the binding between PTHrP and its receptor by administering a genus of substance such as monoclonal antibody, humanized antibody, chimeric antibody, human antibody or binding fragment thereof that binds to human PTHrP (1-34) of SEQ ID NO: 75 as well as monoclonal antibody produced by the hybridoma deposited as FERM BP-5631, wherein the low vasopressin levels as resulted from malignant cancer would include the method of inhibiting the binding between PTHrP and a receptor thereof in claim 11 of the '194 patent comprising administering the humanized antibody that binds specifically to human PTHrP1-34 of the issued patent (species) wherein the humanized antibody is an agent for suppressing hypercalcemia or hypophosphatema associated with malignant tumor.

Further, given the method of the '194 patent teaches the same antibody to treat the same patient population, the method of the '194 patent inherently has the same effects such as maintaining or increasing low vasopressin level wherein the low levels of vasopressin is associated with cancer. As defined in instant specification, "a decrease in

vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Claim 4 is included in this rejection because the '194 patent also teaches modified antibody by amino acid substitution such as version b of the humanized antibody (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). Claim 6 is included in this rejection because the '194 patent also teaches antibody produced by the same deposited hybridoma FERM BP-5631 (see col. 27, lines 29-36, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

It is noted that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

20. Claims 4, 9-10, 16, 19, 25-26 and 28 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 (of record) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising administering to the patient a binding fragment of an anti-PTHrP antibody instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a modified form the fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that bind specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining or increasing low vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent

that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules leas to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

It is noted that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

21. Claims 25-26 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will

lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the monoclonal, human antibody, chimeric or humanized PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

Applicants' arguments filed 7/9/07 have been fully considered but are not found persuasive.

It is noted that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

22. The following new grounds of rejections are necessitated by the amendment filed 7/9/07.

23. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

24. Claims 16, 19-22 and 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is indefinite because of the phrase "and allowing the *substance* to inhibit the binding between PTHrP and its receptor," in line 4; it cannot be determined whether the "substance" still part of the claimed limitation. Further, the "substance" in claim 16 at line 4 has no antecedent basis because the term "substance" in claim 16, line 2 has been deleted.

Claim 16 is incomplete for failing to achieve the goal set forth in the preamble. The preamble of claim 16 recites "a method of inhibiting the binding between PTHrP and a receptor thereof" but ends with "thereby maintaining or increasing low vasopressin levels".

Claim 26 is incomplete for failing to achieve the goal set forth in the preamble. Further, it is not clear as to under which condition that when administering to a patient at least one anti-parathyroid hormone related protein 1-34 (anti-PTHrP) or binding fragment thereof that it maintains low vasopressin level or under which condition that it increases low vasopressin level. Is the vasopressin level found in blood or in posterior pituitary gland in the brain? The specification at page 3 line 12 discloses low blood vasopressin level.

25. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is new matter.**

The recitation of "the method of inhibiting the binding between PTHrP and a receptor thereof ...wherein the antibody is **human** antibody" has no support in the specification and the claims as originally filed. The specification discloses monoclonal antibody that binds to PTHrP (1-34) of SEQ ID NO: 75, humanized, chimeric binding fragment thereof for a method of inhibiting the binding between PTHrP and its receptor or a method of ameliorating the low blood vasopressin level. The specification does not disclose any human antibody that binds to PTHrP (1-34) of SEQ ID NO: 75 as now amended.

27. No claim is allowed.

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

30. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 14, 2007

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600